DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 29, 2008 has been entered.

2. Claims 34-49 are pending.

3. Claim 37 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 34-36 and 38-49, drawn to a composition comprising dead *E. coli* containing therein at least one modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslink IgE as compared with the wild-type peanut allergen are being acted in this Office Action.

5. Claims 35-36 are objected to for reciting non-elected embodiments.

6. The substitute specification filed February 29, 2008 to incorporate essential material into this application from 09/141,220 is effective and has been entered.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-36 and 39-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising dead *E. coli.* comprising at least one modified peanut allergen whose amino acid sequence is identical to that of a wild-type allergen Ara h1, Ara h2 or Ara h3, except that the modified allergen has at least one mutation in an IgE site such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen Ara h1 protein encoded by SEQ ID NO: 1, Ara h2 protein encoded by SEQ ID NO: 2 or Ara h3 encoded by SEQ ID NO: 3, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier and a pharmaceutically acceptable carrier for treating peanut allergy, **does not** reasonably provide enablement for a composition comprising dead *E. coli.* comprising any "modified allergen", any modified food allergen, any modified peanut allergens other than Ara h1, Arah2 and Arah3, any modified milks allergen, any modified eggs, any modified seafood, any modified nuts, any modified dairy product, any modified fruit allergens, except that the modified allergen has at least one mutation in any IgE binding site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein the modified allergen is encapsulated inside the dead E coli as set forth in claims 34-36 and 39-49 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions to peanut in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 34 and 39-49 are broadly drawn to a composition comprising dead *E. coli* comprising a genus of modified allergen whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-

type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 35 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified food allergen whose amino acid sequence is identical to that of a wild-type food allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 36 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified peanut allergen whose amino acid sequence is identical to that of a wild-type peanut allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Enablement is not commensurate in scope with claims as how to make any modified allergen mentioned above encapsulated inside the dead *E. coli* for a composition for treating or preventing any allergy, any allergy such as any food allergy, and any peanut allergy.

At the time of filing, the specification discloses only modified peanut allergens Ara h1, Ara h2 and Ara h3 whose IgE site has at least one mutation in an IgE binding site such that the modified peanut allergen has reduced IgE binding, see page 49-50 Table 4-6. The specification discloses only the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in a mouse subject. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed pharmaceutical composition is to treat and to *prevent* peanut allergy. The specification discloses only modified peanut allergens Ara h1, Ara h2 and Arah3 wherein the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared to wild-type allergen Ara h1, Ara h2 or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, respectively. Further, the specification at page 33 also discloses the levels of allergen release varied and was dependent on the expression vector and protein tested. In general, more Ara h2 was released than

Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of IgG1 and IgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response".

There is insufficient guidance as to the structure of any modified allergen without the amino acid sequence and where such amino acid sequence differs from the undisclosed wild-type allergen sequence. A protein without the amino acid sequence has no structure, much less function. Further, IgE epitope analysis using peptide fragments is useful when the antigen is recognized by patients' serum sequentially according to its primary sequence. However, IgE mainly recognizes the conformation, but not the primary sequence of the allergen.

Aalberse et al (J Allergy Clin Immunol 106: 228-238, 2000; PTO 892) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular). Given the existing knowledge in the art concerning IgE epitopes have high degree of variability within the genus of allergen, there is sufficient guidance as to which amino acid within the IgE binding site to be made such that the claimed genus of modified allergen has reduced IgE binding.

As exemplified by the teachings of Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE

binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Given the unlimited number of modified allergen, modified allergen in any foods, any food such as peanut and the limited in vivo working example, it is unpredictable which undisclosed modified allergen encapsulated inside the dead *E coli* in the claimed composition is effective for treating any allergy. Without the amino acid sequence of any and all modified allergen and the corresponding the cDNA encoding said modified allergen, one of skilled in the art cannot make the recombinant modified allergen encapsulated inside the dead *E coli* for the claimed composition, let alone for *preventing* allergy in the absence of in vivo working example demonstrating such modified allergen could prevent any allergy.

Chatel et al, of record, teach various factors such as the nature of the allergen, the genetic background of mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the genetics of the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al, of record, teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified allergens, modified food allergens, modified peanut allergens expressed in the dead *E coli* in the claimed composition, there is insufficient *in vivo* working example demonstrating the claimed composition is effective for treating any and all allergy.

Even if the wild-type peanut allergens are limited to Ara h1, and Ara h2 encoded by SEQ ID NO: 1 and 2, respectively, Kleber-Janke et al (Protein Expression and Purification 19: 419-424, 2000; PTO 892) teach the level of expression of peanut allergens using BL21(DE3) *Escherichia coli* host cells depends on the nature of the peanut allergen. Kleber-Janke et al teach cDNA encoding Ara h1 and Ara h2 subcloned into the expression vector pET-16b (Novagen) that uses the T7 RNA polymerase-responsive promoter resulted in *ineffective* expression of Ara h1, Ara h2 and Ara h6 in conventional BL21(DE3) *Escherichia coli* (see page 419, col. 2, first full paragraph, in particular). The reason for the ineffective expression of wild-type Ara h1, Ara h2 and Ara h6 in BL21(DE3) was due to high levels of AGG/AGA in Ara h1, Ara h2 and Ara h6 and the least use arginine codons AGG/AGA in *E. coli* (see abstract, page 419, col. 2, in particular).

Finally, the specification discloses immunizing mice with heat killed *E. coli* expressing three different recombinant peanut allergens resulted in three different outcomes (see page 34 of instant specification). In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 34-36 and 39-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34 and 39-49 are broadly drawn to a composition comprising dead *E. coli* comprising a genus of modified allergen whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 35 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified food allergen whose amino acid sequence is identical to that of a wild-type food allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 36 is broadly drawn to a composition comprising dead *E. coli* comprising a subgenus of modified peanut allergen whose amino acid sequence is identical to that of a wild-type peanut allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Claim 38 encompasses a composition comprising dead *E. coli* comprising a species of modified peanut allergen whose amino acid sequence is identical to that of a wild-type peanut allergen Ara h1, Ara h2 or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, except that the modified peanut allergen Ara h1, Ara h2 or Ara h3 has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-

type allergen wherein modified allergen is encapsulated inside the dead *E. coli* and a pharmaceutical acceptable carrier.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification does not reasonably provide a **written description** for any composition comprising dead *E. coli*. comprising at least any one "modified allergen", any modified allergen such as any modified allergens found in any foods, any peanut allergens other than modified peanut allergens Ara h1, Ara h2 and Ara h3, any modified milk, any modified eggs, any modified seafood, any modified nuts, any modified dairy products, any modified fruits, any modified venoms, or any modified latex whose amino acid sequence is identical to any wild-type allergen, except that the modified allergen has any mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link as compared with the wild-type allergen as set forth in claims 34-36 and 39-49 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions with allergy in a subject.

At the time of filing, the specification discloses only modified peanut allergens Ara h1, Ara h2 and Ara h3 whose IgE site has at least one mutation in an IgE binding site such that the modified peanut allergen has reduced IgE binding, see page 49-50 Table 4-6. The modified peanut allergens are expressed in *E. coli* and render dead by heat. The specification discloses the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in mice. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed composition is to treat and to *prevent* any allergy. The instant specification at page 33 also discloses the level of allergen released varied and was dependent on the expression vector and protein tested. In

general, more Ara h2 was released than Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of lgG1 and lgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response". The specification disclosed the complete structure of only three species of peanut allergen within the scope of the claimed modified peanut allergen Ara h1, Ara h2 and Ara h3 whose wild-type amino acid sequences are encoded by SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3. The specification discloses the reduction to practice of only three modified peanut allergens Ara h1, Ara h2 and Ara h3.

The specification does not describe other members of the modified food allergen or modified allergen by structure. The specification does not describe the complete structure of any modified allergen, any modified Food allergen or any modified peanut allergens other than the modified peanut allergens Ara h1, Ara h2 and Ara h3 as shown in Table 4, 5 and 6, respectively. Common structural attribute, i.e. sequence of IgE binding sites of species of modified peanut Ara h1 allergen in the genus modified allergen are not described. The specification does not describe the common structure of any IgE binding site among the genus of modified wild-type allergen, the subgenus of modified food allergen and other species of modified peanut allergen. There is no teachings regarding which amino acids within the binding site among the genus of wild type allergen can vary and still result in reduced ability to bind to or cross-link IgE other than the modified peanut allergen Ara h1, Ara h2 and Ara h3. There is no disclosed correlation between structure and function.

The state of the art at the time of filing is such that IgE epitope on allergens are conformational.

Aalberse et al (J Allergy Clin Immunol 106: 228-238, 2000; PTO 892) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular).

While general knowledge in the art may have allowed one skill in the art to modify protein by random deletion, substitution, or addition, there is no census in the art about mutation in IgE epitope would led to reduce IgE binding or crosslinking.

Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) teach that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in

particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy.

Because the described modified peanut allergens in the dead *E coli* is not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus of modified allergen or the subgenus of modified food allergen.

Accordingly, one of skill in the art would conclude that applicant was not in procession of the claimed genus because a description of only a composition comprising modified peanut allergen Ara h1, Ara h2 and Ara h3 expressed in dead *E coli* of this genus is not representative of the modified peanut allergen, or modified food allergen or modified allergen to show that the applicant would have been in possession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 34, 35 and 36.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1103, Friday April 11, 2004.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 34-36, 38-45 and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892).

The WO 99/38978 publication teaches a composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical to the ones to be incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The claimed invention differs from the teachings of the reference only in that the composition comprising modified allergen encapsulated in *E coli* wherein the *E coli* is dead instead of alive and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page 1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFNγ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

The '799 patent teaches the use of *E coli* bacteria as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The '799 patent teaches the antigen or allergen of interest in the *E coli* can be engineered to transport across the E coli cytoplasmic

membrane end ended up in the periplasmic space (see col. 14, line 29-31, in particular). The bacterial cell is formulated for administered orally in enteric-coated capsules (see col. 13, line 4-6, in particular).

The '141 patent teaches a method of modifying anaphylactogens which reduces toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about 50 to 100 °C to reduce toxicity of the antigens (see col. 1, lines 8-65, col. 2, line 1-10, in particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide H_2O_2 (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* bacteria that expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the bacteria with heat such as heating from about 50 to 100 °C as taught by Fenton or the '141 patent or Lecberc et al or kill by oxidizing agent such as hydrogen peroxide as taught by the '141 patent to avoid any technical and ethical issues without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen because peanut is highly anaphylactic and the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria *E coli* expressing modified food allergen because Vrtala et al teach killing the

microorganism that expressed modified allergen can avoid the ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria as vaccine carrier because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine since antigen presenting cell such as macrophage can phagocytose the bacteria *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat-killed *E coli* bacteria because Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use bacteria E coli as a vaccine carrier because the '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to kill bacteria with heat because the '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. Claim 43 is included in this rejection because it is obvious that IgE binding to modified peanut allergen cannot be detected without disrupting the dead *E coli* with urea since the modified allergen can be engineered to located as inclusion bodies located within the cytoplasm as taught by Fenton et al, or can be engineered to transport across the *E coli* cytoplasmic membrane end ended up in the periplasmic space instead of cytoplasm as taught by the '799 patent or Leclerc et al. Claim 44 is included in this rejection because a composition is a composition, irrespective of

its intended use such as adapted for rectal administration. The heat-killed *E coli* in the pharmaceutical composition as taught by Fenton et al could be adapted for rectal administration.

12. Claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claims 34-36, 38-45 and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892) mentioned above and further in view of WO 92/14487 (newly cited published September 1992; PTO 892) and US Pat No 6,270,723 (of record, filed Oct 2, 1998; PTO 892), Komanapalli et al (newly cited, Appl Microbil Biotechnol 49: 766-769, 1998; PTO 892) and/or Ingram et al (newly cited, J Bacteriology 144(2): 481-488, Nov 1980; PTO 892).

The combined teachings of the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and/or Leclerc et al have been discussed supra.

The claimed invention in claim 46 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed using a chemical instead of heat.

The claimed invention in claim 47 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohols instead of heat.

The WO 92/14487 publication teaches a method of safely killing *E coli* bacteria expressing various colonization factor antigens by chemical treatment such as mild or diluted formalin-treated *E coli* for use as a whole cell vaccine (see page7-8, page 19, line 26, in particular). The WO 92/14487 publication teaches the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page 8, lines 7-9, in particular).

The '723 patent teaches various methods of killing *bacteria* by chemical treatment such as alcohol (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or

pressure sterilization (ozone) to inactivate bacteria such as *E coli* for pharmaceutical composition (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ozone induced lipid oxidation in *E coli* and leakage of cytoplasmic contents (see abstract, see Figs 5 & 6, in particular).

Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Ingram et al teach increasing concentrations of alcohol such as ethanol and hexanol progressively inhibits the growth of E coli and hexanol was a much more potent inhibitor of growth than was ethanol (see page 482, col. 2, in particular). Ingram et al teach ethanol prevented the assembly of cross-linked peptidoglycan while hexanol did not inhibit such cross-linking, see page 485, col. 2, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to kill any recombinant modified peanut allergen producing *E. coli* bacteria for a pharmaceutical composition given the highly anaphylactic nature of the peanut allergen as taught by the WO 99/38978 publication by means chemical treatment such as mild or diluted formalin-treatment as taught by the WO 92/14487 publication or diluted alcohol (see col. 1, line 21, in particular), or diluted bleach (see col. 10, line 39-40, in particular) as taught by the '723 patent instead of heat as taught by Fenton et al or by different types of alcohol as taught by Ingram or by ozone as taught by Komanapalli et al to preserve the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication.

One having ordinary skill in the art would have been motivated to kill *E coli* bacteria expressing modified peanut allergen because peanut allergens are highly anaphylactic as taught by the WO 99/38978 publication. One having ordinary skill in the art would have been motivated to kill *E coli* bacteria expressing modified peanut allergen with any conventional chemical because the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as maintaining greater stability of the antigen against degradation in the intestinal milieu as taught

by the WO 92/14487 publication (see page 8, lines 7-9, in particular). The '723 patent teaches chemical treatment such as iodine, bleach, ozone, or alcohol can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular). Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* (see page 767, col. 2, results, Fig. 1, in particular). The motivation to kill the modified peanut allergen expressed in *E coli* for a pharmaceutical composition is obvious given the ethical problems for using live bacteria as allergy vaccines in patients as taught by Vrtala et al (see page 293, col. 2, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed 11/3/06 have been fully considered but are not found persuasive.

Applicants' position is that that the '723 patent teaches methods for sterilizing, decontaminating, or disinfecting materials and the advantages of this pressure based method is that it avoids denaturing proteins as compared to heat or chemical treatment and thereby enhances the immunogenicity of the resulting vaccine (see col. 5, lines 30-36). If anything, the '723 patent therefore teaches away from the prior art uses of chemical and heat.

In response to the argument that the '723 patent teaches solely cryobaric method for preparing vaccines is misleading. The '723 patent also teaches various traditional methods for bacterial inactivation or killing such as the use of chemical disinfectants (formaldehyde, glutaraldehyde, alcohols, mercury compounds, quaternary ammonium compounds, halogenated compounds, solvent/detergent systems, or peroxides (see col. 1, back ground of invention, in particular). As evidence by the teachings of WO 99/38978 publication, the use of mild or diluted formalin can safely kill *E coli* bacteria expressing various antigen of interest for use as a whole cell vaccine and the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page7-8, page 19, line 26, page 8, lines 7-9, in particular). It is within the purview of one ordinary skill in the pharmaceutical art to kill recombinant bacteria for a pharmaceutical composition by means of heat as taught by Fenton et al or by chemical means such as mild

formalin-killed bacteria for a vaccine as taught by WO 92/14487 publication or mild alcohol or bleach as taught by the '723 patent. The motivation to kill the modified peanut allergen expressed in *E coli* for a pharmaceutical composition is obvious given the ethical problems for using such live bacteria as allergy vaccines in patients as taught by Vrtala et al (see page 293, col. 2, in particular). Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ozone-induced lipid oxidation in *E coli* and leakage of cytoplasmic contents (see abstract, see Figs 5 & 6, in particular).

Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Ingram et al teach increasing concentrations of alcohol such as ethanol and hexanol progressively inhibits the growth of *E coli* and hexanol was a much more potent inhibitor of growth than was ethanol (see page 482, col. 2, in particular). Ingram et al teach ethanol prevented the assembly of cross-linked peptidoglycan while hexanol did not inhibit such cross-linking, see page 485, col. 2, in particular.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 34-36 and 38-49 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-45 of copending Application No. 10/728,051. Although the conflicting claims are not identical, they are not patentably distinct from each other because an issuance of a patent to instant application drawn to a *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the wild-type allergen is found in nature in foods, in peanuts, milk, eggs, seafood, nuts, dairy products, fruit, as well as modified allergen is located in the cytoplasm or periplasm of the dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol would include the pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: l, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 10/728,051.

Thus the issuance of a patent to instant application (genus) would include the pharmaceutical composition of 10/728,051 (specie). The issuance a patent to copending application 10/728,051 (species) anticipates the claimed composition of instant application (genus).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
April 11, 2008